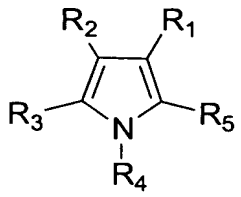
CLAIMS:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof, wherein

R_1 and R_2 are independently selected from optionally substituted aryl and optionally substituted heteroaryl;

R_3 is selected from hydrogen, optionally substituted alkyl, -N=CR'", –C(O)R', –C(O)NR'R", –NR'R", optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, wherein R' and R" are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heterocycle;

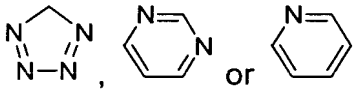
R_4 is selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, and –SiR'"R""R"" wherein R'", R"", and R"" are each an independent straight chain or branched $C_{1\text{-}5}$alkyl, or R_3, R_4 and the –C–N– to which R_3 and R_4 are connected together form an optionally substituted 5- or 6-membered ring;

R_5 is selected from optionally substituted alkyl, –C(O)OR', –C(O)NR'R", C(O)NHNHC(O)R_6, –SO_2NR'R", –C(O)R', –NR'R", nitrile, nitro, halo, and optionally substituted heterocycle, or R_4, R_5 and the –C–N– to which R_4 and R_5 are connected together form an optionally substituted 5- or 6-membered ring;

R_6 is selected from H, alkyl, optionally substituted aryl; and

with the provisos that

(1) R_1 and R_2 are not both optionally substituted phenyl;

(2) if either R_1 or R_2 is optionally substituted phenyl or 3-thienyl, and the other is unsubstituted  , then R_3 is not hydrogen, unsubstituted alkyl, $-(CH_2)_3OH$, $-(CH_2)_3PH$, $-(CH_2)_3OMs$, or $-(CH_2)_2N(CH_2)_2O(CH_2)_2$, and R_5 is not unsubstituted alkyl, $-(CH_2)_3OH$, $-(CH_2)_3PH$, $-(CH_2)_3OMs$, or $-(CH_2)_2N(CH_2)_2O(CH_2)_2$; and

(3) R_4 doesn't form a fused ring with both R_3 and R_5.

2. The compound of Claim 1 wherein R_1 is substituted with a group selected from hydrogen, amino, alkyl substituted amino, aryl substituted amino, hydroxy, methoxy, phenyl ether, S-alkyl, halogen, trifluoromethyl, and nitro.

3. The compound of Claim 1 wherein R_2 is substituted with a group selected from hydrogen, amino, alkyl substituted amino, aryl substituted amino, hydroxy, methoxy, phenyl ether, S-alkyl, halogen, trifluoromethyl, and nitro.

4. The compound of Claim 3 wherein R_2 is heteroaryl having 1-3 N.

5. The compound of Claim 1 wherein R_3 is selected from hydrogen, alkyl, aryl, heteroaryl, heterocycle, and -NR'R", wherein R' and R" are independently selected from hydrogen, alkyl, aryl, and heterocycle.

6. The compound of Claim 1 wherein R_4 is hydrogen or alkyl.

7. The compound of Claim 6 wherein R_4 is hydrogen or methyl.

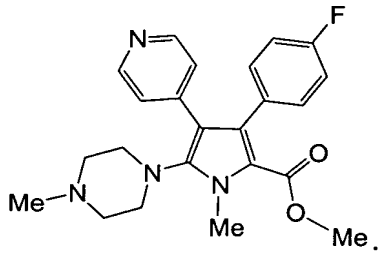
8. The compound of Claim 1 wherein R_5 is selected from alkyl, -C(O)OR', -C(O)NR'R", nitrile, and heterocycle.

9. The compound of Claim 8 wherein R_5 is selected from is selected from -$(CH_2)_nOR'$, -$(CH_2)_nNR'R'''$, -$(CH_2)_nCOOR'$, -$(CH_2)_nCONR'R''$, -NHCOR', and ester isosteres.

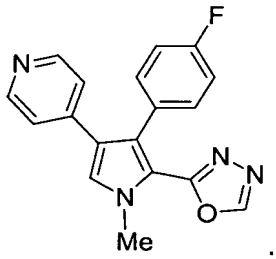
10. The compound of Claim 9 wherein R_5 is selected from oxadiazole, 1,2,4-triazole, 1,2,4-triazol-3-ol, isoxazol-3-ol, imidazolidine-2,4-dione, 4H-[1,2,4]thiadiazol-5-one, oxazole, and [1,3,4]oxadiazole.

11. The compound of Claim 10 wherein R_5 is 4H-[1,2,4]oxadiazole-5-thione or 4H-[1,2,4]oxadiazol-5-one.

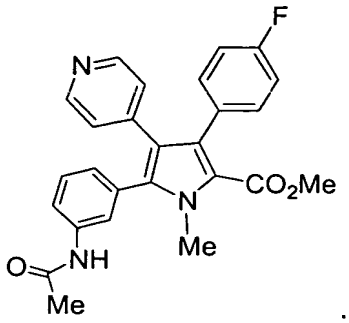
12. The compound of claim 1 having the structure



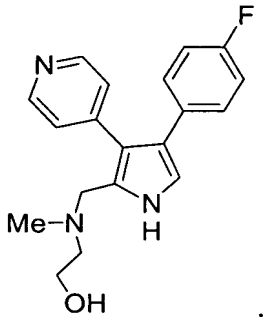
13. The compound of claim 1 having the structure



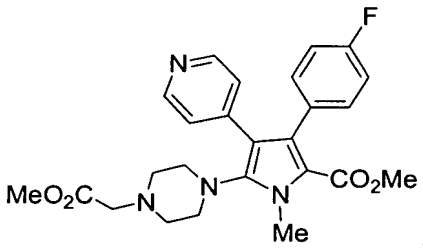
14. The compound of claim 1 having the structure



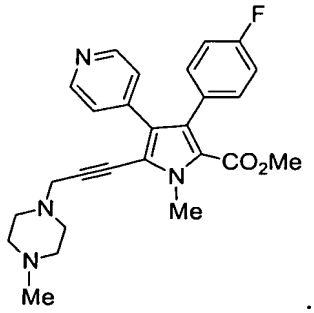
15. The compound of claim 1 having the structure



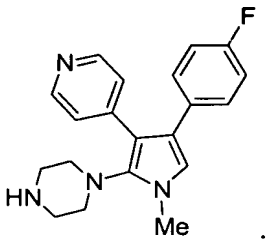
16. The compound of claim 1 having the structure



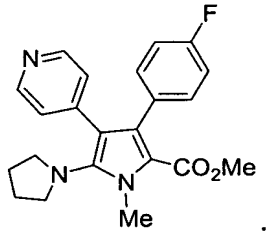
17. The compound of claim 1 having the structure



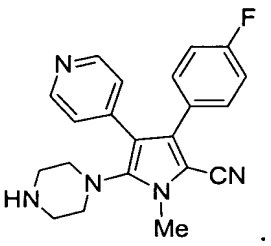
18. The compound of claim 1 having the structure



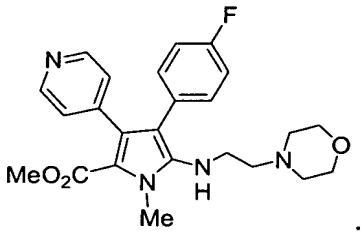
19. The compound of claim 1 having the structure



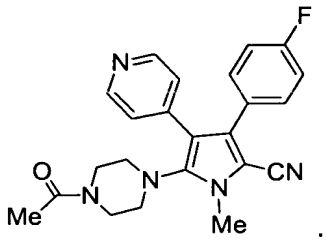
20. The compound of claim 1 having the structure



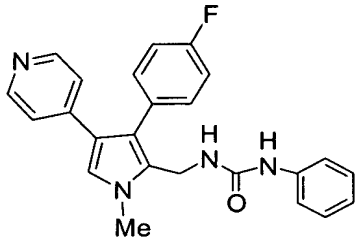
21. The compound of claim 1 having the structure



22. The compound of claim 1 having the structure



23. The compound of claim 1 having the structure



24. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

25. A method of treating a subject having a disorder ameliorated by reducing TNF-α production and/or p38 activity in appropriate cells, which comprises administering to the subject a therapeutically effective dose of the pharmaceutical composition of claim 24.

26. The method of claim 25, wherein the disorder is an inflammatory disorder.

27. The method of claim 25, wherein the disorder is selected from the group consisting of rheumatoid arthritis, osteoporosis, osteoarthritis, allergic inflammation, periodontal disorder, inflammatory bowel disorder, septic shock, insulin-dependent diabetes mellitus, non-insulin-dependent diabetes, cachexia, pulmonary fibrosis, myasthenia gravis, Crohn's disease, hepatitis, primary biliary cirrhosis, acute pancreatitis, allograph rejection, glioblastoma, alopecia areta, psoriasis, ischemia, congestive heart failure, restenosis, atherosclerosis, systemic lupus erythematosus, nephritis, Guillain-Barre Syndrome, viral myocarditis, HIV replication, T-cell depletion in HIV infection, cognitive deficits

induced by neuronal inflammation, multiple sclerosis, stroke, neuropathic pain, HIV dementia and Alzheimer's disease.

28. The method of claim 27, wherein the disorder is rheumatoid arthritis.

29. A method of preventing an inflammatory response in a subject, comprising administering to the subject a prophylactically effective amount of the pharmaceutical composition of claim 24 either preceding or subsequent to an event anticipated to cause the inflammatory response in the subject.

30. The method of claim 29, wherein the event is selected from the group consisting of an insect sting and an animal bite.